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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/616,821	07/10/2003	Mark S. Sands	WSHU 2047.1	2687

321 7590 03/08/2006

SENNIGER POWERS
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EXAMINER	
LI, QIAN JANICE	
ART UNIT	**PAPER NUMBER**
1633	

DATE MAILED: 03/08/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/616,821	SANDS ET AL.	
	Examiner	Art Unit	
	Q. Janice Li, M.D.	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *24 February 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-29* is/are pending in the application.

4a) Of the above claim(s) *12-18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11 and 19-29* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group I, claims 1-11, and 19-29, and species election drawn to hemophilia A, protein FVIII, and cytokine VEGF, is acknowledged. The traversal is on the ground(s) that the claims have a common feature of administering to a subject endothelial progenitor cells comprising a gene encoding a functional protein responsible for a congenital disease, that a search of these claims can be made without serious burden; and the two groups have the same classification. This is not found persuasive because different diseases have distinct etiology and pathogenesis, involves distinct protein as the causative factor. A structural search for a protein responsible for hemophilia A would not overlap with a search for lysosomal storage disease. Not to restrict would require searches for numerous diseases and distinct proteins, which would impose serious search burden on the Office. Thus, it is maintained that each of the Inventions requires a separate search status and consideration. The inventions are mutually exclusive and independent methods for *ex vivo* gene and stem cell therapies. As such the searches for groups II and I are not co-extensive. M.P.E.P. states, "FOR PURPOSES OF THE INITIAL REQUIREMENT, A SERIOUS BURDEN ON THE EXAMINER MAY BE PRIMA FACIE SHOWN IF THE EXAMINER SHOWS BY APPROPRIATE EXPLANATION OF SEPARATE CLASSIFICATION, OR SEPARATE STATUS IN THE ART, OR A DIFFERENT FIELD OF SEARCH AS DEFINED IN MPEP § 808.02" (emphasis added). Therefore, it is maintained that these inventions are distinct due to their

divergent subject matter. Further search of these inventions is not co-extensive, as indicated by the independent search criteria. The requirement is still deemed proper and is therefore made **FINAL**.

Please note that after a final requirement for restriction, the Applicants, in addition to making any response due on the remainder of the action, may petition the Commissioner to review the requirement. Petition may be deferred until after final action on or allowance of claims to the invention elected, but must be filed not later than appeal. A petition will not be considered if reconsideration of the requirement was not requested. (See § 1.181.).

Claims 1-29 are pending, however, claims 12-18 are withdrawn from further consideration by the Examiner, pursuant to 37 CFR 1.142(b), as being drawn to non-elected inventions, there being no allowable generic or linking claim. Claims 1-11, and 19-29 are under current examination.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1, 3-11, 19-22, 27-29 are rejected under 35 U.S.C. 102(e) as being anticipated by *Rafii et al* (US 6,852,533).

Rafii et al teach a method of isolating endothelial stem (progenitor) cells (EPC) according to their surface markers including VEGF (e.g. claim 1), and using such as a gene transfer carrier for treating diseases such as hemophilia A (column 10, line 6). *Rafii et al* teach the endothelial stem cells may serve as a carrier for gene therapy, i.e. introducing a gene into the EPC, wherein the gene is the Factor VIII gene (column 8, lines 48-57); wherein the endothelial stem cells transfected with a gene therapy vector may be naturally or artificially be recruited to the site where the protein expression by the gene is required or new cells are desired by means of cytokines such as VEGF (column 10, lines 13-15, and column 8, lines 39-43); wherein the EPCs may be autologous or heterologous (column 10, lines 22-25).

Accordingly, *Rafii et al* anticipate instant claims.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary.

Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 21, 23-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Rafii et al* (US 6,852,533), in view of *Mardiney III, et al* (USP 6,423,311) and *Storb et al* (Blood 1999;94:2523-9).

The teaching of *Rafii et al* was detailed supra, *Rafii et al* do not mention the pre-conditional regimen (radiation, immunosuppressant) before, during or after EPC transplantation, or cytokine mitogen mentioned in claim 28.

Mardiney III, et al and *Storb et al* supplemented the deficiency by establishing that it was well known in the art, these are necessary steps to control immune rejection, and promote stem cell engraftment (e.g. see claims of the cited patent and the abstract of *Storb et al*).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to combine the method as taught by *Rafii et al* with that of *Mardiney III, et al* and *Storb et al*, with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to so for the sake of a safe and success EPC transplantation. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claims 1, 3-11, and 19-28 are rejected under 35 U.S.C. 103(a) as being unpatentable over *Hoeben et al* (Thromb Haemost 1992;67:341-5) in view of *Dwarki et al* (PNAS 1995;92:1023-7) and *High* (Circ Res 2001;88:137-44).

The claims are drawn to treating a congenital protein deficiency in a subject, wherein the elected species of deficiency is hemophilia A. The method comprises administering to the subject endothelial progenitor cells that comprise a gene encoding a functional form of the protein, and the elected species of the protein is a Factor VIII. In working examples of the specification, the source of EPCs is unfractionated bone marrow cells (Specification, page 22). Thus, bone marrow cells are considered as meeting claim limitation for EPCs for the purpose of applying prior art.

As early as 10 years before instant filing date, *Hoeben et al* teach a method of gene therapy for treating hemophilia A, the method comprises transfecting bone marrow cells with retroviral vector encoding FVIII, and transplanting the transfected bone marrow cells into lethally irradiated mice. Although *Hoeben et al* did not use an immunosuppressive drug such as cyclosporine A, or mention the use of a cytokine such as GM-CSF, it was well known that pre-conditioning of bone marrow prior to stem cell transplantation could be performed by either irradiation or chemotherapeutic agent such as cyclosporine and could include a cytokine to promote stem cell engraftment. *Hoeben et al* fail to demonstrate expression of FVIII *in vivo*, but teach the approach is nevertheless promising in gene therapy of hemophilia upon further development in gene therapy technology.

Dwarki et al and *High* supplemented the deficiency by illustrating the state of the art at around the time of instant priority date with respect to technical development in FVIII expression *in vivo*. *Dwarki et al* transfected various cell

types with a MFG retroviral vector expressing B-domain-deleted FVIII (fig. 1), and achieved efficient expression in all cell types tested (table 1 and column 1, page 1025). *Dwarki et al* go on to teach the level of expression found in a mouse model was close to normal values in man and attribute their success to the vector used, the B-domain deletion of the FVIII, and the routes of administering the transfected cells (e.g. column 1, page 1027).

High reviews the state of the art, and indicates that preclinical studies over the last decade have recently culminated in the initiation of clinical trails of gene transfer for hemophilia (e.g. abstract), and many technical developments have made the *in vivo* FVIII expression possible to the extend that warrants phase I clinical study (e.g. column 1, page 140).

Accordingly, it would have been obvious to one of ordinary skill in the art at the time the invention was made to use the vectors as taught by *Dwarki et al* and *High* in the method taught by *Hoeben et al*, with a reasonable expectation of success. The ordinary skilled artisan would have been motivated to modify the claimed invention because the vectors developed subsequent to *Hoeben et al* publication have proven to be efficient in FVIII expression *in vivo*. Thus, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any

> person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-11, and 19-29 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for intravenous administering to a subject endothelial progenitor cells comprising a nucleic acid encoding a functional FVIII, does not reasonably provide enablement for treating hemophilia A in a subject and administering the EPCs via any route of administration. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The factors to be considered when determining whether the disclosure satisfies the enablement requirements and whether undue experimentation would be required to make and use the claimed invention are summarized in *In re Wands*, (858 F2d 731, 737, 8 USPQ 2d 1400, 1404, (Fed Cir.1988)). These factors include but are not limited to the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability of the art, the breadth of the claims, and amount of direction provided. The factors most relevant to this rejection are the nature of the invention relative to the state of the art and the levels of the skilled in the art, and whether sufficient amount of direction or guidance are provided in the specification to enable one of skill in the art to practice the claimed invention.

The claims are drawn to a therapeutic method of treating a congenital protein deficiency, preferably hemophilia A by administering EPCs expressing

FVIII to a subject in need. The specification teaches that applicant discovered that donor bone marrow-derived EPCs incorporate into the blood vessels of the recipient's normal, nonischemic tissues during the postnatal period, and as a result EPCs may be used in cellular and gene therapy of multiple congenital protein deficiencies, including hemophilia A (Specification, page 8, line 21 to page 9, line 2). The specification administered unfractionated whole bone marrow of transgenic mice expressing a marker protein via intravenous injection, and reported the implanted cells could be found in neovasculature of newborn recipients, and VEGF enhances such neovasculature.

As an initial matter, it is noted prior to the instant filing, *Asahara et al* (Circ Res 1999;85:221-8, IDS) had reported that EPCs of bone marrow origin are responsible for postnatal vasculogenesis in physiological and pathological neovascularization, thus, the asserted "discovery" does not appear to be novel at the time of filing.

Further, the specification fails to teach why increased vasculogenesis is beneficial for treating hemophilia A, and how to control the vasculogenesis so that it does not lead to unwanted neovascularization. The specification fails to teach how to deliver the EPCs to a prenatal subject, and why such is necessary. Thus, one would not know how to use the invention beyond art known use of bone marrow cells as gene delivery vehicle.

As to treating hemophilia A, the specification only prophetically contemplates such. Thus, the enablement of the claimed invention relies on the knowledge of the skilled in the art. Turning to the state of the art at a post-filing

date, *Lozier* (Semin Hematol 2004;41:287-96) teaches, animal models of hemophilia, large and small, are important tools for investigating and safety testing of gene therapy vectors, but gene therapy of hemophilia remains an investigational method with many obstacles to overcome before it can be widely used as a real world treatment for hemophilia. To this end, the specification fails to teach how to overcome the art known hurdles, and fails to reduce to practice showing that hemophilia A could indeed be treated in any way by the claimed method. Thus, the specification fails to provide an enabling disclosure for what is now claimed.

Therefore, in view of the limited guidance, the lack of predictability of the art and the breadth of the claims, one skill in the art could not practice the invention without undue experimentation as it is broadly claimed.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 21 is vague and indefinite because of the claim recitation, "heterologous". It is unclear what the term refers to in the context of the claims, e.g. the diversity with the EPC population or the origin of the cells, and thus the metes and bounds of the claims are uncertain.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Q. Janice Li** whose telephone number is 571-272-0730. The examiner can normally be reached on 9:30 am - 7 p.m., Monday through Friday, except every other Wednesday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Dave T. Nguyen** can be reached on 571-272-0731. The **fax** numbers for the organization where this application or proceeding is assigned are **571-273-8300**.

Any inquiry of formal matters can be directed to the patent analyst, **William Phillips**, whose telephone number is (571) 272-0548.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

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Q. JANICE LI, M.D.
PRIMARY EXAMINER

Q. Janice Li, M.D.
Primary Examiner
Art Unit 1633

QJL
March 6, 2006